Estimation of minimal clinically important difference for the Tardive Dyskinesia Impact Scale, a tardive dyskinesia-specific patient-reported outcome

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BACKGROUND

- Tardive dyskinesia (TD) is an involuntary, hyperkinetic movement disorder in which patients experience abnormal involuntary movements. TD is associated with long-term exposure to dopamine receptor-blocking agents, including antipsychotics and drugs that treat gastrointestinal conditions.[1,2]
- The Abnormal Involuntary Movement Scale (AIMS) is a clinician-reported outcome. The AIMS total score is the current gold standard for evaluating efficacy in TD clinical trials; however, AIMS is not always routinely used in clinical practice and does not focus on the patient perspective related to the functional, social, and emotional effects of TD.[2,3]
- The Tardive Dyskinesia Impact Scale (TDIS) is a novel, TD-specific patient-reported outcome (PRO) measure that assesses the daily physical, social, and emotional impact of TD symptoms.[7]
- The minimal clinically important difference (MCID) of a measure indicates the difference in score that provides patients with a specific degree of clinically meaningful improvement.[4]
- No MCID has been determined for the TDIS.

OBJECTIVE

- Establish an MCID for the TDIS using data from two 48-week, phase 3 trials of valbenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of TD in US adults: KINECT™ 3 (NCT02274558)[5] and KINECT™ 4 (NCT02405091).[6]

METHODS

Overview of TDIS

- TDIS is a reliable and valid PRO measure containing 11 items that assess the patient's daily functioning over the prior 7 days using a 5-point Likert scale that ranges from 0 (no impact) to 4 (most impact).
- For example, the first TDIS question asks "Over the past 7 days, how difficult was it for you to speak due to the uncontrollable movements of your tongue, jaw, lips, or mouth?" and respondents would choose 0 (not at all), 1 (slightly), 2 (moderately), 3 (very), or 4 (extremely).
- The TDIS overall score ranges from 0 to 44, with a higher score indicating increased impairment and disability due to TD.
- Each of the 11 items maps to the domains specified in **Table 1**.

Table 1. TDIS conceptual framework

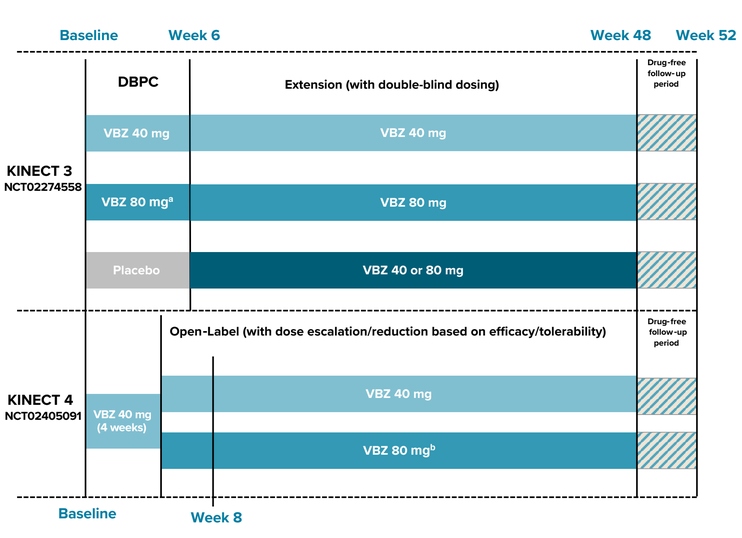
Domain	Item
Mouth/Throat function	1. Speech
	2. Mouth noises
	3. Swallowing
Dexterity	4. Gripping
	5. Writing
Mobility	6. Walking
	7. Balance
Pain	8. Leg pain
Social	9. Unwanted attention
Emotional	10. Embarrassed
	11. Self-conscious

Key: TDIS – Tardive Dyskinesia Impact Scale.

Study design

- Data from KINECT 3 , a randomized, placebo-controlled, double-blinded trial and KINECT 4, an open-label trial investigating the long-term effects of valbenazine in adults with TD, were used in these analyses (**Figure 1**)[5,6]:
  - KINECT 3 included patients assigned in a 1:1:1 ratio to daily placebo, valbenazine 40 mg/day, or valbenazine 80 mg/day for 6 weeks, followed by an extension period of valbenazine 40 mg/day or 80 mg/day for 42 weeks.
  - Patients enrolled in KINECT 4 initially received valbenazine 40 mg/day and had their doses increased to 80 mg/day at Week 4 in response to drug efficacy and tolerability, for a total treatment time of 48 weeks.
  - Across both studies, participants receiving valbenazine 80 mg/day were allowed to have their dose reduced to 40 mg/day, but patients who were unable to tolerate 40 mg/day were subsequently removed from the study.
  - Both studies had a 4-week, drug-free follow-up period.

Figure 1. KINECT 3 and KINECT 4 study design



Key: DBPC – double-blind, placebo-controlled; VBZ – valbenazine.

Participants

Key inclusion criteria:

- Adult patients (aged 18-85 years) with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and psychiatrically stable per their Brief Psychiatric Rating Scale (BPRS) score.
- Diagnosed with neuroleptic-induced TD for ≥3 months before screening per DSM-IV.
- Qualitative diagnosis of moderate or severe TD at screening per external reviewer.

Key exclusion criteria:

- Any clinically significant unstable medical condition (per investigator judgment) within 1 month before screening.
- Elevated psychiatric scores (BPRS ≥50); elevated schizophrenia symptoms (positive and negative syndrome scale ≥70 or Calgary depression scale for schizophrenia ≥10); elevated depression or mania scores for mood disorder (Montgomery-Asberg Depression Rating Scale >13 or Young Mania Rating Scale score of >10).
- Concurrent movement disorder characterized as more pronounced than TD.
- High risk of active suicidal ideation, suicidal behavior, or violent behavior.

Analyses

- The MCID analyses were conducted in the following populations:
  - Patients from KINECT 3 (N=225) and KINECT 4 (N=163) who received ≥1 dose of valbenazine and had ≥1 postbaseline AIMS assessment.
- Both anchor- and distribution-based approaches were used to estimate an MCID for TDIS.[10]

Anchor-based approach

- Anchor-based approach using single-item Clinical Global Impression of Change (CGI-TD) and single-item Patient Global Impression of Change (PGIC).[8,9]
  - Both items are rated on a scale of 1 to 7 as follows: very much improved (1); much improved (2); minimally improved (3); no change (4); minimally worse (5); much worse (6); very much worsened (7).
- CGI-TD and PGIC scores of minimally improved (score =3) were used as anchors.
- Based on these anchors, a calculated MCID was determined based on the TDIS mean score change from baseline to Week 6 in KINECT 3 and Week 8 in KINECT 4 in all patients with CGI-TD and PGIC scores =3.
  - In KINECT 3 , patients receiving valbenazine 40 mg, valbenazine 80 mg, and placebo were combined for the analysis.

Distribution-based approach

- Distribution-based approaches included the standardized response mean (SRM) and the standard error of measurement (SEM).[10]
  - SRM assesses change in relation to sample variation and is independent of sample size. SRM values of 0.2, 0.5, and 0.8 represent small, moderate, and large change, respectively.[10]
  - SEM assesses the precision of the instrument and uses a reliability coefficient of the instrument. The baseline standard deviation of TDIS was used to calculate the SEM. Values of 1.00 to 2.77 SEM have been suggested in the literature for defining clinically meaningful differences.[10]

RESULTS

- **Table 2** shows the baseline characteristics for the treatment groups in KINECT 3 and KINECT 4; the mean baseline score for TDIS was similar between groups.

Table 2. Baseline characteristics for KINECT 3 and KINECT 4

	KINECT 3 N=225	KINECT 4 N=163
Age, mean (SD), years	56 (10)	57 (10)
Male, n (%)	121 (54)	86 (53)
Race, n (%)		
White	128 (57)	110 (68)
Black/African American	86 (38)	48 (29)
Primary psychiatric diagnosis, n (%)		
Schizophrenia/Schizoaffective disorder	148 (66)	119 (73)
Mood disorder	77 (34)	44 (27)
TDIS score, mean (SE)	15.1 (0.6)	16.0 (1)

Key: SD – standard deviation; SE – standard error; TDIS – Tardive Dyskinesia Impact Scale.

- In patients receiving valbenazine, the trajectory over 48 weeks shows TDIS total score improved over time.
- Mean TDIS change from baseline for KINECT 3 and KINECT 4 is shown in **Table 3.**

Table 3. Change in TDIS at Week 6 (KINECT 3) and Week 8 (KINECT 4)

	N	Δ from baseline	SEM
KINECT 3[a]	225	−4.0	0.5
KINECT 4	163	−5.6	0.6

Key: SEM – standard error of the mean; TDIS – Tardive Dyskinesia Impact Scale.
[a]Treatment groups (valbenazine 40 mg, valbenazine 80 mg, and placebo) were combined for analysis.

Anchor-based results

- The majority of patients had mean CGI-TD and PGIC scores of ≤3 in both trials (71% and 74%) at Week 6 for KINECT 3 and 86% at Week 8 for KINECT 4 (**Table 4**).

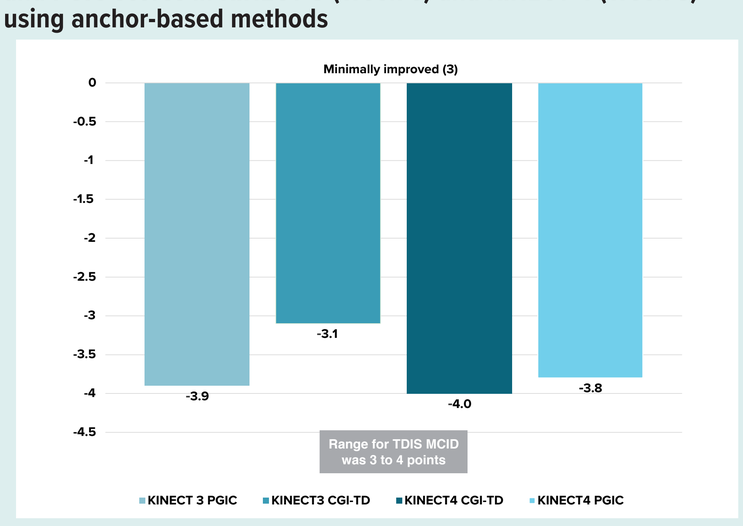
Table 4. Frequency of CGI-TD and PGIC scores ≤3 or =3 in KINECT 3 (Week 6) and KINECT 4 (Week 8)

	KINECT 3[a]		KINECT 4	
	N	%	N	%
CGI-TD =3 (minimally improved)	87	43%	56	38%
CGI-TD ≤3 (minimally to very much improved)	143	71%	127	**86%**
PGIC =3 (minimally improved)	83	41%	47	32%
PGIC ≤3 (minimally to very much improved)	149	74%	128	**86%**

Key: CGI-TD – Clinical Global Impression of Change-Tardive Dyskinesia; PGIC – Patient Global Impression of Change.
[a]Treatment groups (valbenazine 40 mg, valbenazine 80 mg, and placebo) were combined for analyses using anchor-based methods.

- In patients with CGI-TD and PGIC scores =3, the change in TDIS total score in both trials ranged from −3.1 to −4.0 points at 6 and 8 weeks, respectively (**Figure 2**).
- For patients with CGI-TD and PGIC of ≤3, the change in TDIS total score in both trials ranged from −3.1 to −10.2 points at 6 and 8 weeks, respectively.
  - Change in mean TDIS scores were the highest for patients with CGI-TD and PGIC of 1 (very much improved) in both KINECT 3 and KINECT 4 (range −7.7 to −10.2).

Figure 2. TDIS mean change for minimally improved (3) CGI-TD and PGIC scores in KINECT 3 (Week 6) and KINECT 4 (Week 8) using anchor-based methods



Key: CGI-TD – Clinical Global Impression of Change-Tardive Dyskinesia; MCID – minimal clinically important difference; PGIC – Patient Global Impression of Change; TDIS – Tardive Dyskinesia Impact Scale.

Distribution-based results

- The SEM was −1.66 for KINECT 3 and −1.68 for KINECT 4 using the baseline standard deviation, falling within the suggested range for defining clinically meaningful differences.[10]
- The SRM was −0.58 for KINECT 3 and −0.74 for KINECT 4, which suggests a moderate to large effect size change.[10]

MCID estimate

- Using results from anchor- and distribution-based approaches yielded an MCID estimate of 3 to 4 points based on the anchors of CGI-TD and PGIC scores =3.

LIMITATIONS

- Data were collected in the context of TD clinical trials examining the efficacy of valbenazine; results may vary if the TDIS was evaluated in a more naturalistic population.
- The data evaluated the effects of valbenazine in the TD patient populations in the 2 trials in the US and Puerto Rico; it is unknown whether the findings are generalizable to other patient populations with TD, populations outside the US, or with other therapies.

CONCLUSIONS

- This is the first evaluation of MCID for the TDIS in a clinical setting.
- Data from KINECT 3 and KINECT 4 showed that a **3- to 4-point change** in TDIS total score may be used as an **MCID** in TD patients.
- The use of both anchor- and distribution-based analyses strengthen this finding.
- Determining MCID is useful for interpreting how much change in TDIS scores is considered clinically meaningful and provides a benchmark for clinicians and researchers.

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